899. *An Examination of the Rutaceae of Hong Kong. Part V.* A New Coumarin, Avicennin, from the Bark of* Zanthoxylum avicennae.

By H. R. Arthur and C. M. Lee.

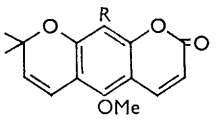
Degradation reveals that avicennin, $C_{20}H_{22}O_4$, a coumarin isolated from the bark of *Zanthoxylum avicennae*, is a substituted 2,2-dimethylchromenocoumarin.

It was reported earlier [1,2] that avicennin, a new yellow coumarin, occurs in the root-bark and bark of *Zanthoxylum avicennae*. Whilst avicennin, $C_{20}H_{22}O_4$, was shown not to contain a phenolic group, a methoxyl group was demonstrated by a Zeisel determination. Catalytic hydrogenation showed two reducible double bonds. Evidence that avicennin is a coumarin was obtained from its behaviour and that of its tetrahydro-derivative towards alkali, from the positive result of a fluorescence test,[3] and by reference to its

* Part IV, *J.*, 1959, 4010.

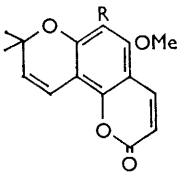
[1] Arthur, Hui, and Ng, *J.*, 1959, 4007.
[2] Arthur, " Proceedings of the Phytochemical Symposium," Kuala Lumpur, 1957, p. 123.
[3] Feigl, Feigl, and Goldstein, *J. Amer. Chem. Soc.*, 1955, **77**, 4162.

infrared spectrum which shows, like that of xanthoxyletin (I; R = H), strong absorption at 1745 cm.$^{-1}$ characteristic of the >C=O stretching vibration of the δ-lactone system.[4]

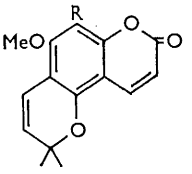


(I); R = H

(II); R = $CH_2 \cdot CH{:}CMe_2$



(III); R = $CH_2 \cdot CH{:}CMe_2$



(IV); R = $CH_2 \cdot CH{:}CMe_2$

Oxidation of avicennin gave α-hydroxyisobutyric acid as do 2,2-dimethylchromens [5] and this, in the absence of evidence for a furan ring, suggests that avicennin is a substituted 2,2-dimethylchromenocoumarin. The isolation of phloroglucinol monomethyl ether, acetone, and acetic acid from hydrolytic fission of avicennin accounts for the four oxygen atoms of the molecule and provides additional evidence for the 2,2-dimethylchromenocoumarin structure (cf. xanthoxyletin [5] and xanthyletin [6]).

The C_5H_9 residue is likely to be an isopentenyl group, which is common in plant coumarins. This substituent would account for one of the catalytically reducible double bonds (the other being in the chromeno-ring—cf. xanthoxyletin [5] which gives dihydroxanthoxyletin on catalytic reduction) and would account for the ozonolysis products, acetone and the aldehyde, $C_{17}H_{16}O_5$. Comparison of the infrared spectra (at 3030 cm.$^{-1}$ and 960—800 cm.$^{-1}$) of avicennin, tetrahydroavicennin, xanthoxyletin (I), and dihydroxanthoxyletin suggests [7] the absence of aromatic hydrogen in avicennin and thus indicates that a substituent is present in the aromatic ring, which is fully substituted, having five positions previously accounted for by the lactone ring of the coumarin, the chromeno-ring, and the methoxyl substituent.

It is suggested that avicennin, which forms a dimer, has one of the structures (II, III, or IV).

Experimental

Analyses were by Dr. Zimmermann, Melbourne. M. p.s were taken on a gas-heated copper block and are uncorrected. Paper used for chromatography was Whatman No. 1, and the solvent was methanol–heptane.

Isolation of Avicennin.—Dry bark (1·2 kg.) was extracted (Soxhlet) with hot methanol (2 × 12 l.) for 4 hr. The combined extracts were concentrated to 3 l. and left for 24 hr. The wax was collected and the filtrate was concentrated to 0·6 l. A crystalline mixture [1] of hesperidin and diosmin was collected and the filtrate was then distilled to dryness under reduced pressure. The residue was extracted with hot chloroform (3 × 0·5 l.); the extract was shaken several times with 8% aqueous sodium hydroxide and then with 15% sulphuric acid, and then washed with water, and dried. Removal of the chloroform gave a brown oil which on trituration with methanol deposited yellow crystals (3 g.) which were recrystallised seven times from ethanol. Yellow elongated prisms (0·3 g.) of *avicennin*, m. p. 141—142°, $[\alpha]_D$ = 0·0° (*c* 4·0 in $CHCl_3$) separated (Found: C, 73·8; H, 6·5; OMe, 10·3%; *M*, 338. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·7; OMe, 9·5%; *M*, 326). Avicennin gave a red colour with concentrated sulphuric acid. It was insoluble in water and in aqueous sodium hydroxide but dissolved in aqueous alcoholic sodium hydroxide, and on removal of the alcohol, it remained in solution. It was precipitated unchanged from the latter solution by passage of carbon dioxide.

Hydrolytic Fission of Avicennin.—Avicennin (3·0 g.) was boiled with 25% aqueous sodium hydroxide (100 ml.) for 4 hr. and then filtered. The filtrate, after acidification with hydrochloric acid and saturation with ammonium sulphate, was extracted nine times with ether. The washed and dried extract was evaporated. The reddish-brown oil, after having been

[4] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1956, p. 159.
[5] Bell, Robertson, and Subramaniam, *J.*, 1936, 627.
[6] Bell and Robertson, *J.*, 1936, 1828.
[7] Bellamy, *op. cit.*, p. 55 *et seq.*

extracted with sodium hydrogen carbonate solution (*A*), was essentially phloroglucinol monomethyl ether (0·25 g.) (Found: OMe, 22·9. Calc. for $C_7H_8O_3$: 1OMe, 22·1%). It gave the di-*p*-nitrobenzoate as needles, m. p. 197—198° (Found: C, 58·4; H, 3·5; N, 6·4. Calc. for $C_{21}H_{14}O_9N_2$: C, 57·5; H, 3·2; N, 6·4%). Solution (*A*) was acidified with hydrochloric acid and then extracted eight times with ether. On evaporation of the ethereal solution a reddish-brown liquid was obtained. This was boiled with *p*-toluidine (1·2 g.) for 1 hr. The cooled mixture on suitable working-up gave crystals of aceto-*p*-toluidide, m. p. and mixed m. p. 147°. In a second fission avicennin (4·0 g.) and 50% aqueous sodium hydroxide (200 ml.) were heated under reflux for 4 hr. Water (200 ml.) was added to the cooled mixture which was then distilled. The distillate (100 ml.) yielded acetone (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 125—126°).

Ozonolysis of Avicennin.—A slow stream of ozonised oxygen was passed into a solution of avicennin (1·2 g.) in chloroform (100 ml.) for ¾ hr. Removal of the solvent left a residue which was treated with cold water (60 ml.) for 18 hr. then heated on the steam-bath for 20 min. The mixture was extracted with ether and the ethereal extract, after treatment with sodium hydrogen carbonate solution, was distilled to dryness. The yellow oil gave an *oxime* (0·006 g.) as rectangular plates (from ethanol), m. p. 194—195° (Found: C, 65·0; H, 5·5; N, 4·3. $C_{17}H_{17}O_5N$ requires C, 64·7; H, 5·4; N, 4·4%). Avicennin (0·5 g.) was also ozonised in glacial acetic acid (50 ml.) for ½ hr. The mixture was steam-distilled and the distillate was treated with 2,4-dinitrophenylhydrazine. The orange-yellow precipitate could not be purified by crystallisation or by chromatography on alumina (benzene solution) but in a paper chromatogram, spots identical with those of formaldehyde 2,4-dinitrophenylhydrazone (R_F = 0·18; 21·5°) and acetone 2,4-dinitrophenylhydrazone (R_F = 0·50; 21·5°) were observed. The steam-distillate obtained in repeating the ozonolysis in acetic acid yielded formaldehyde dimedone (0·008 g.), m. p. and mixed m. p. 185—186° after one crystallisation from 70% aqueous ethanol, and the steam-distillate, examined with 2,4-dinitrophenylhydrazine after removal of formaldehyde, yielded acetone 2,4-dinitrophenylhydrazone (0·004 g.), m. p. and mixed m. p. 125—126°.

Tetrahydroavicennin.—Avicennin (0·4 g.) in ethanol (250 ml.) was hydrogenated at room temperature and above atmospheric pressure in the presence of Adams catalyst (0·04 g.). Hydrogen (approx. 2 mols.) was quickly absorbed. After removal of the catalyst and concentration of the solution, rhombic crystals were deposited which on recrystallisation from methanol or light petroleum gave *tetrahydroavicennin*, m. p. 81—82° (Found: C, 72·8; H, 7·9; OMe, 9·8%; *M*, 360. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·8; OMe, 9·4%; *M*, 330). The product did not dissolve in aqueous sodium hydroxide, but dissolved in aqueous alcoholic sodium hydroxide from which it could be precipitated by passage of carbon dioxide.

Tetrahydroavicennic Acid.—Application of Canter and Robertson's method and variations of it for converting a coumarin into the *O*-methyl ether of the corresponding cinnamic acid failed to yield a pure product from avicennin. This procedure was, however, successfully applied to tetrahydroavicennin: tetrahydroavicennin (1·5 g.) was boiled with 20% aqueous sodium hydroxide (50 ml.) for 20 min.; water (40 ml.) was added and the heating continued for 10 min. The cooled mixture was filtered. The filtrate was acidified with concentrated hydrochloric acid, mixed with ice, and kept below 10°. The precipitate, on crystallisation from benzene, gave pale yellow prisms of *tetrahydroavicennic acid*, m. p. 150—151° (decomp.) (Found: C, 69·0; H, 8·4; OMe, 9·2. $C_{20}H_{28}O_5$ requires C, 69·0; H, 8·0; OMe, 8·9%). This product gave a reddish colour with alcoholic ferric chloride and decolorised aqueous potassium permanganate and a solution of bromine in carbon tetrachloride.

Degradative Oxidation of Avicennin.—Oxidation of avicennin with potassium permanganate in acetone, with concentrated nitric acid, or with alkaline hydrogen peroxide did not yield products which could be purified. Oxidation with chromic anhydride in acetic acid yielded acetone (identified as the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 126—127°).

3% Aqueous sodium hydroxide (30 ml.) was added to methanolic avicennin (2·0 g. in 100 ml.). After removal of methanol, sodium hydroxide (1 g.) and water (170 ml.) were added. During ½ hr. potassium permanganate (12 g.) in water was added until persistence of a pink colour. The mixture was then warmed (steam-bath), decolorised with sulphur dioxide, and then extracted with ether. The aqueous layer, after acidification, was again extracted with ether, and this ethereal solution was dried and evaporated. The residue obtained was treated with boiling light petroleum; the solution obtained yielded needles of α-hydroxyisobutyric acid,

m. p. 76—78° undepressed in admixture with an authentic sample obtained from 1,1,1-trichloro-2-methylpropan-2-ol (Found: C, 46·8; H, 7·5%; *M*, 125. Calc. for $C_4H_8O_3$: C, 46·2; H, 7·7%; *M*, 104).

Dimerisation of Avicennin.—Avicennin (0·7 g.) was heated under reflux with ethylene glycol (40 ml.) for 1 hr. The cooled solution deposited a yellow solid which, after four recrystallisations from ethanol, gave pale yellow rectangular plates of *avicennin dimer*, m. p. 206—208° (Found: C, 74·3; H, 6·5; OMe, 10·7%; *M*, 676. $C_{40}H_{24}O_8$ requires C, 73·6; H, 6·7; 2OMe, 9·5%; *M*, 652).

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